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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/575,554	05/22/00	MUNIA B	ISPH-0463

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EXAMINER	
FREDMAN, J	

ART UNIT	PAPER NUMBER
1655	6

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/575,554	Applicant(s) Monia et al
	Examiner Jeffrey Fredman	Group Art Unit 1655

☐ Responsive to communication(s) filed on _____ .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-23* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-23* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Double Patenting

1. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claim 6 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 1 of prior U.S. Patent No. 5,872,242. This is a double patenting rejection.

3. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

4. Claims 1, 4, 5 and 7-22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 5,872,242. Although the conflicting claims are not identical, they are not patentably distinct from each other because the species claims of U.S. Patent No. 5,872,242 anticipate the larger genus claims 1, 4, 5 and 7-22 of the current application. These species necessarily render the genus claim obvious since they fall directly within the scope of the genus claim.

5. Claims 1, 2, 5 and 7-23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,576,208.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the species claims of U.S. Patent No. 5,576,208 anticipate the larger genus claims 1, 2, 5 and 7-23 of the current application. These species necessarily render the genus claim obvious since they fall directly within the scope of the genus claim.

6. Claims 1, 2, 5 and 7-23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5,582,986. Although the conflicting claims are not identical, they are not patentably distinct from each other because the species claims of U.S. Patent No. 5,582,986 anticipate the larger genus 1, 2, 5 and 7-23 of the current application. These species necessarily render the genus claim obvious since they fall directly within the scope of the genus claim.

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

> person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-5 and 7-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

10. Claims 1-5 and 7-23 are rejected as lacking an adequate written description regarding the antisense oligonucleotides which function to inhibit ras. The claims are drawn to antisense oligonucleotides "which is capable of inhibiting ras expression (claim 13)" The specification teaches that an antisense oligonucleotide possesses the functional characteristics of hybridizing to a transcript and prevents translation of the transcript (page 3, line 13 to page 4, line 1). It is well known in the art that out of the large number of nucleic acid sequences complementary to a given transcript, only a portion are effective at inhibiting expression of the gene as shown by Stein et al (Nature Biotechnol. (March 1999) 17:209) who states "It has been a frequent, perhaps even universal, observation (e.g. see refs (omitted)) that for every eight or so oligomers tested against any one particular target, only one will be 'active'. In fact, the ratio of 1 success in 8 tested seems to be the best ratio attained, some researches report 1 success in 12 or , or even 1 in 15 (page 209, column 2)". Effective sequences can not be predicted and must be identified experimentally and as discussed in the quote above, the fraction of molecules that effectively inhibits expression of a transcript is estimated at only 1 in every 8 to 15 of those tested experimentally. Gewirtz et al

(Proc. Natl. Acad. Sci. (April 1996) 93:3161-3163) characterizes finding effective antisense sequences as a "hit or miss process" (page 3161, columns 2 & 3). The specification provides guidance on how one may empirically screen for effective antisense molecules (pages 8-14), but this guidance is not sufficient to allow one to envision the structures of specific, functional molecules. For those sequences which are shown to have effect, such as those on page 38 in Table 11 of the specification, possession is evident. However, in undefined broad claims, in an technical discipline which requires specific sequences for function, the artisan would not be able to envision the breadth of the claimed invention based on the description provided and, therefore, would not conclude that applicant was in possession of the invention as claimed at the time the specification was filed.

11. The above rejection is made in view of the publication of the "Interim Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, ¶ 1, 'Written Description' Requirement", published in the Federal Register (Vol. 63, No. 114, pp. 32,639-32,645) on 15 June 1998, and are available at www.uspto.gov and at the Federal Register web site.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1, 3 and 5-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bos, Daaka et al., Hall et al (Nucleic Acids Res. 13(14):5255-5268) and Saison-Behmoaras et al., each in view of Uhlmann et al., Agrawal et al. and Inoue et al., and further in view of Smith. Bos discloses antisense oligonucleotides to human H-ras and Ki-ras and to the specific regions of ras genes (codons 12 and 61) that are mutated in the activated forms of these genes (see Column 4, line 26 to Column 5, line 10). Bos teaches that the molecules of the invention may be labeled and used in methods to detect the activated forms of ras, by either hybridizing to single-stranded genomic DNA fragments or to RNA isolated from cells or tissue to be tested. Hall teaches the sequence of N-ras from which the specific antisense molecules are derived as well as the importance of the mutations at codons 12 and 61 (page 5256, and page 5264, figure 4). Daaka et al. teach antisense molecules to the translation initiation codon site of the H-ras gene and the use of the antisense molecules to inhibit H-ras expression in and the growth of transformed 3T3 cells. Saison-Behmoaras et al. teach oligonucleotides that specifically hybridize to the codon 12 region

of H-ras and methods of using the oligos to inhibit expression of the gene. Thus, the three primary references all provide teachings of oligonucleotides directed against the claimed regions of H-ras or Ki-ras and their use to inhibit expression of the gene and growth of transformed cells, or to detect the activated genes. The primary references do not teach oligos having phosphorothioate linkages, chimeric oligonucleotides containing runs of phosphodiester-linked oligodeoxynucleotides flanked by RNase H-resistant oligonucleotides, modifications to increase the affinity toward the target, the specific oligonucleotide sequences of the instant invention or the method of treating an animal by administering the oligonucleotides of the invention. Uhlmann et al. teach a wide variety of modifications to antisense oligonucleotide structures, including phosphorothioate backbone modifications and the use of 2'-modified ribonucleotides such as 2'-O-methyl nucleotides. Uhlmann et al. disclosed motivation for making oligos with these modifications to increase stability and decrease costs. They also disclosed that 2'-O-methyl modified oligonucleotides formed duplexes with RNA that were more thermostable than DNA-RNA hybrids, thus suggesting that 2'-O-methyl oligos had increased affinity for their RNA targets.

Inoue et al. and Agrawal et al. each teach the RNase H sensitivity or resistance of duplexes formed from RNA and various modified oligonucleotides. Agrawal discloses that phosphodiester and phosphorothioate backbones confer sensitivity to RNase H, whereas oligos with methylphosphonate and some other backbone structures confer resistance to RNase H. Inoue et al. disclosed chimeric antisense oligonucleotides containing resistant 2'-O-methyl residues flanking at least 4 deoxynucleotide residues. These molecules, after forming a duplex with

complementary RNA, promoted specific cleavage by RNase H in the tetradeoxynucleotide region of the duplex. Smith et al. disclose the use of antisense oligonucleotides, with or without modified backbones, against oncogenes or genes that are differentially expressed in tumor cells, as a treatment for cancer. Thus, they disclose a method of treating cancer by administering appropriate antisense oligos to inhibit the growth of tumor cells or kill the tumor cells. Although the oligonucleotides that are claimed by specific sequence are not specifically disclosed in the art, the regions of the genes to which they are targeted are clearly taught in the art. The specific sequences would be derived by one of ordinary skill in the art making a variety of antisense oligonucleotides targeted at the taught regions. Thus, one of ordinary skill in the art would have known at the time the invention was made to modify the teachings of the primary references by making oligonucleotides that have modified backbones, stretches of deoxynucleotides that are sensitive to RNase H digestion and 2' modified ribose moieties as disclosed by Uhlmann et al., Agrawal et al. and Inoue et al., in order to obtain the advantages of increased stability, target affinity and target destruction taught by the secondary references. One of ordinary skill in the art would further have known to use the oligos in methods of preventing expression of the ras gene, inhibiting tumor cell growth and treating an animal having an activated ras gene, and in methods of detecting different forms of the ras gene, as suggested by the primary references and Smith for the obvious advantages of slowing or stopping tumor growth and diagnosing the presence or absence of activated forms of the ras gene, which are linked to cancer. Therefore, the invention

as a whole was *prima facie* obvious in the absence of evidence or secondary considerations to the contrary.

Further, Bos provides the requisite sequence information for Ki-ras. Hall provides the requisite sequence information for N-ras. Motivation is provided by several of these references. Saison-Behmoaras states "It has been found that 10-20% of human tumors have a mutation in one of the three ras genes (Ha-ras, Ki-ras, N-ras) leading to the production of p21 ras oncoproteins, which are thought to play an important role in the transformed phenotype (page 1111, column 1)". Here, Saison-Behmoaras discloses the equivalence of the three ras oncogenes and provides a strong and direct motivation to inactivate each of these genes, since they are found activated in 10-20% of human tumors. Saison-Behmoaras continues "In order to study the biological effects of ras expression in the context of molecular biology of ras-dependent pathway and to provide a rational basis for the development of antitumor drugs we are investigating the use of antisense oligonucleotides and their modified analogues, which upon hybridization to complementary mRNA sequences, interfere with translation and thus can be employed for sequence-specific control of gene expression. In an attempt to inhibit the expression of an oncogene, application of antisense oligonucleotides has proved to be a powerful tool (page 1111, column 1 to column 2)". This quote demonstrates that Saison-Behmoaras provides a motivation to utilize antisense oligonucleotides to achieve the goal, as noted above, of inactivation of ras oncogenes, since antisense oligonucleotides were known to be a powerful tool to interfere with translation and gene expression of the ras oncogenes and since the antisense oligonucleotides could provide a rational

basis for drug development. Further motivation is provided by Daaka, who states "The ras family of mammalian protooncogenes includes three members, termed Ha-ras, Ki-ras, and N-ras, that are likely to play a fundamental role in basic cellular functions based on their high degree of conservation throughout eukaryotic evolution (ref omitted). The amino acid sequence of the ras gene products all contain GTP-binding consensus regions and are thought to be localized to the inner surface of the plasma membrane (ref omitted). In mammals, ras proteins have been implicated in cellular proliferation (ref omitted) and terminal differentiation (ref omitted). Point mutations in ras oncogenes that alter the enzymatic properties and/or cause overexpression of the ras p21 oncoprotein may be causatively or closely linked ot the onset of some types of human tumors (refs omitted) (page 267, columns 1 and 2)." Daaka here also motivates the ordinary practitioner to inactivate mutated ras proteins, including any of the three equivalents, Ha-ras, Ki-ras or N-ras. Daaka also teaches the use of antisense methodologies to perform this inactivation (page 267, column 2 to page 268, column 1). Bos et al also motivates the inactivation of the ras oncogene, though Bos does not suggest an antisense mechanism " The human gene family consists of three members: the H-ras, K-ras and the N-ras gene (1) These genes code for related proteins of 21kD, which are located at the inner face of the cell membrane (36) and are thought to be involved in transducing signals from cell surface receptors to their intracellular targets (37). A significant portion of tumor cell lines and fresh tumor tissue has been found to possess an activated ras gene. Such genes are characterized by their ability to induce oncogenic transformation of mouse 3T3 cells. In most cases so far analyzed the activation is due to a point

mutation in the 12th or 61st codon of a ras gene resulting in a single amino acid substitution in the gene product (column 1, lines 14-26)".

These three references each note the linkage and potential causative nature of ras oncogenes with human tumors. Each reference discloses that three different, but functionally and structurally equivalent ras oncogenes termed Ha-ras, Ki-ras and N-ras are involved in human tumors. Saison-Behmoaras and Daaka explicitly motivate the inactivation of these proteins by antisense mechanisms to inhibit tumor formation and growth. These references thus provide explicit motivation for the ordinary practitioner to inactivate Ki-ras, Ha-ras and N-ras in order to inhibit tumor formation and growth.

Conclusion

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeff Fredman, Ph.D. whose telephone number is (703) 308-6568.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Jeffrey Fredman
Primary Patent Examiner
Art Unit 1655

March 20, 2001